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CYTOPROTECTIVE EFFECT OF GROWTH HORMONE RELEASING HORMONE AGONIST IN CARDIAC STEM CELLS

Poster Contributions
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Background: Our group has recently shown that potent growth hormone releasing hormone (GHRH) agonists are cardioprotective in cardiac injury due to myocardial infarction (MI) and that this effect is receptor-mediated. The number of c-kit+ cardiac stem cells (CSCs) was increased in animals treated with the GHRH agonist JI38, suggesting that this agonist might have an effect on these progenitor cells.

Methods: The expression of GHRH receptor (GHRHR) was determined in mouse, rat and porcine CSCs and mesenchymal stem cells (MSCs) origin (3-5 animal isolates from each species) using fluorescence activated cell sorting. Porcine CSCs were treated with the GHRHR agonist JI38 and the antagonist MIA-602 for evaluation of their effect on proliferation and survival of porcine CSCs after exposure to hydrogen peroxide. Proliferation was assessed by immunodetection of thymidine analogue incorporated during DNA synthesis and cell death was detected by Annexin V staining.

Results: CSCs and MSCs from the three animal species tested were 96-98% positive for the expression GHRHR as compared to positive and negative control cancer cell lines. Treatment of porcine CSCs with 250nM JI38 significantly increased proliferation rate by 2-fold in JI38 treated cells (3.4 + 0.7) vs. vehicle control (1.7 + 0.2) ($p<0.05$, $n = 3$). Similar effects on CSCs proliferation were observed after treatment with novel GHRHR agonists, supporting these observations. Experiments with the GHRHR antagonist MIA-602 showed a trend of reversal of agonist effect in proliferation rate (2.2 + 0.6). Overnight exposure of porcine CSCs to hydrogen peroxide increased the expression of Annexin V as expected. Pretreatment of CSCs with 50nM JI38 reduced the number of cells stained positive for this early marker of cell death by 33 + 2.2 % ($p<0.02$, $n = 4$), showing that JI38 promoted CSCs survival.

Conclusion: Together these findings confirm for the first time the expression of GHRHR in CSCs and MSCs. GHRH agonist treatment promotes CSCs proliferation and enhance survival. Accordingly, activation of GHRH receptor signaling pathways represents a novel therapeutic approach to protect and locally stimulate endogenous CSC population, promoting cardiac repair.